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[54] Title of the Invention: Novel Azithromycin Crystals and Method for Their Manufacture

[57] Abstract

This invention relates to novel azithromycin crystals and to a method for their manufacture.

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CLAIMS

1. Novel azithromycin crystals characterized in that said crystals are short and columnar.

2. A method for the manufacture of the azithromycin crystals described in Claim 1 which method includes: crystallization of azithromycin monohydrate in a water-soluble organic solvent and water.

3. A method as described in Claim 2 in which the azithromycin crystals described in Claim 1 are obtained by crystallizing azithromycin monohydrate in a mixture of a water-soluble organic solvent and water.

4. A method as described in Claim 2 in which the azithromycin crystals described in Claim 1 are obtained by first dissolving azithromycin monohydrate in a water-soluble organic solvent, after which it is again crystallized in water.

5. A method as described in Claims 3 and 4 in which the molar ratio of azithromycin monohydrate : water-soluble organic solvent : water is 1 : 10-15 : 30-1500.

6. A method as described in Claim 2 in which the water-soluble organic solvent is selected from methanol, acetone, N,N-dimethylformamide, N,N-dimethylformamide [sic], dimethylsulfoxide, cyclobutyl sulfone, hexamethyl phosphoryl amide, acetonitrile, dioxolane, ethylene glycol, dimethyl ether, piperidine and mixtures of them.

7. A method as described in Claim 6 in which the water-soluble organic solvent is selected from acetone.

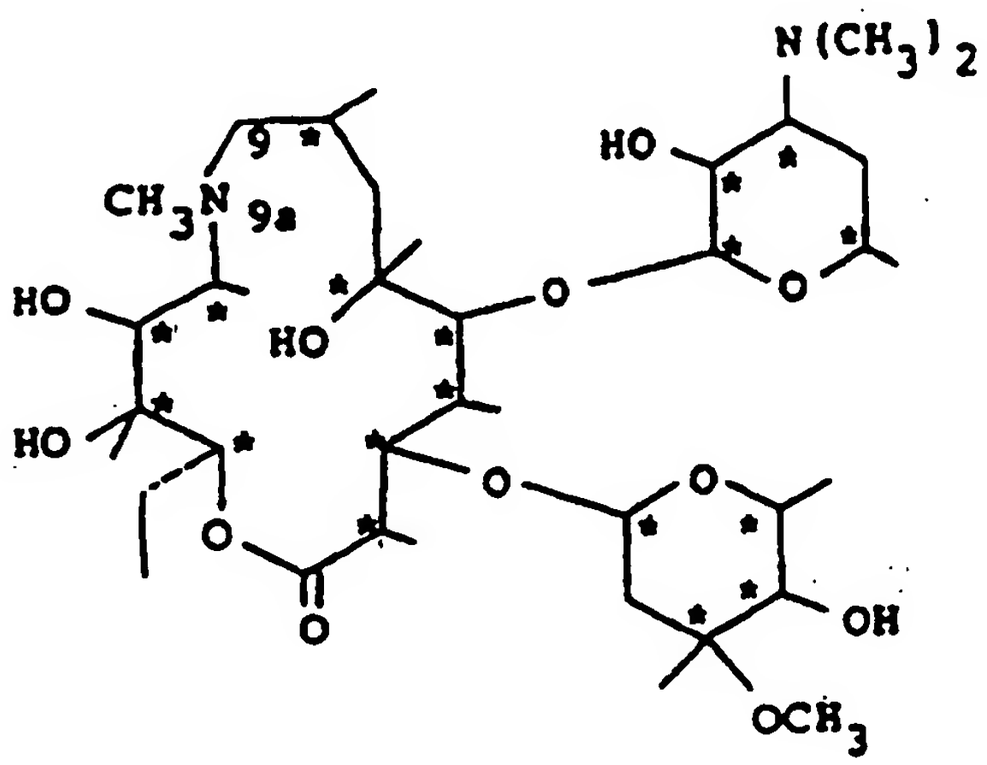
8. A method for the use of the azithromycin crystals described in Claim 1 in preparing medicinal drug preparations which includes mixing the azithromycin crystals described in Claim 1 directly with a carrier for a drug or vehicle to form standard medicinal drug preparations.

SPECIFICATION

Novel Azithromycin Crystals and a Method for Their Manufacture

This invention relates to novel azithromycin crystals, a method for their manufacture and their use in various types of medicinal drug preparations. More specifically speaking, this invention relates to azithromycin crystals of superior fluidity and stability, a method for the preparation of said crystals and their use for preparing medicinal drug preparations.

Azithromycin (chemical name: 9-deoxo-9a-aza-methyl-9a-homoerythromycin A) is an erythromycin derivative and is a broad-spectrum antibiotic. Azithromycin has a broader antibacterial spectrum than erythromycin, is resistant to acids and is suited to oral use. Its pharmacokinetic characteristics are ideal and superior. The structure of azithromycin is shown by formula I below.



I

The azithromycin shown in formula I is a known compound. American patents US 4,474,768 and US patent 4,517,359 disclosed a method for the preparation of azithromycin monohydrate. However, because of the hygroscopic properties of azithromycin monohydrate, it is very unstable when used in preparations and there are very great limitations in its clinical use. European patent EPO 298,650 disclosed an azithromycin dihydrate, which is more stable than azithromycin monohydrate, and a method for its manufacture. Because the azithromycin dihydrate that is prepared by this method is in a powdery state, it cannot be used directly in preparations. In addition, the tetrahydrofuran and C_6-C_7 aliphatic hydrocarbon reagents that are used in said method are comparatively expensive, the difference between the melting points of the tetrahydrofuran and C_6-C_7 aliphatic hydrocarbons is comparatively small, it is difficult to recover the solvents and it is difficult to control the water content in the products.

The objective of this invention was to find novel azithromycin crystals of better fluidity and stability and a simpler, more economical method of preparation.

The inventors conducted broad-ranging and intensive research and unexpectedly discovered that azithromycin monohydrate underwent crystallization in a mixture of water-soluble organic solvents and water; that novel, short, columnar azithromycin crystals could be obtained in this way; that said crystals had superior fluidity and stability; and that they could be used directly in the preparation of medicinal drugs. This invention was perfected on the basis of this discovery.

The first objective of this invention relates to a new type of azithromycin crystals. Said crystals are short, columnar crystals that have superior fluidity and stability and that can be used directly in the preparation of medicinal drugs.

More specifically speaking, the novel azithromycin crystals of this invention contain 4 to 6% of water and have the X-ray diffraction characteristics indicated below.

2—THETA	*INT*	*d*	*I/IO*
6.180	111.0	14.290	4
7.820	3292	11.296	11
9.800	29070	9.018	100
11.180	5050	7.908	17
12.420	3638	7.121	13
14.580	1936	6.071	7
15.300	3922	5.786	13
15.660	2262	5.654	8
17.060	2197	5.193	8
18.780	1909	4.721	7
19.000	2783	4.667	8
19.540	1909	4.539	7
19.820	2569	4.476	9
20.400	3600	4.350	12

Their infrared spectrum characteristics are indicated below:

IR(cm^{-1}): 3429 (OH), 2969 (-CH_3, -CH_2, -CH-), 1728 (C=O), 1459 (-CH_3, -CH_2, -CH-), 1183 (C-O-C), 1050 (C-OH, -C-O-D).

The stability tests of the novel azithromycin crystals of this invention are described in the examples that are presented subsequently.

The second objective of this invention relates to a method of preparing the novel azithromycin crystals of this invention, which method includes crystallization of azithromycin monohydrate in a mixture of a water-soluble organic solvent and water.

More specifically speaking, the method of this invention is to dissolve azithromycin monohydrate in a mixture of hot organic solvent and water, after which it is slowly cooled until crystals are precipitated, or to dissolve azithromycin monohydrate in an organic solvent, after which water is gradually added until crystals precipitate. The dissolution temperature of azithromycin monohydrate and the crystallization temperature of the novel azithromycin crystals of this invention are not critical and can be from room temperature to the boiling point of the solution. Priority is given to room temperature and a quantity of organic solvent with which the entire azithromycin monohydrate solution is completely dissolved as the standard and to a quantity of water whereby most of the crystals (greater than 78%) are precipitated as the standard, generally, azithromycin monohydrate : water (molar ratio) = 1 : 10-15 : 30-1500. Finally, the crystals are filtered and are vacuum-dried at room temperature to a water content of 4 to 6%.

The water-soluble organic solvents that are used in the method of this invention are selected from methanol, acetone, N,N-dimethylformamide, N,N-dimethylformamide [sic], dimethylsulfoxide, cyclobutyl sulfone, hexamethyl phosphoryl amide, acetonitrile, dioxolane, ethylene glycol, dimethyl ether, piperidine and mixtures of them.

The third objective of this invention relates to the application of the novel azithromycin crystals of this invention in the preparation of drug preprations which includes the direct use of the novel azithromycin crystals of this invention in the preparation of antibiotic preparations.

The examples presented below are intended as further descriptions of this invention but do not limit this invention in any way.

1. Stability tests:

The novel azithromycin crystals of this invention (indicated by A in the following table) were allowed to stand at a relative humidity of 20% and a relative humidity of 90% and changes in the water content of the crystals were tested for at 0, 12, 24, 36, 48, 60 and 72 hours. The

azithromycin dihydrate crystals described in EPO 298,650 (indicated by B in the following table) were tested in the same way under the same conditions. The results are shown in Table 1.

Table 1

Comparison of Stability of Azithromycin Crystals of This Invention (A) and the Azithromycin Dihydrate Crystals of EPO 298,650 (B)

Time (hrs)	20% relative humidity		90% relative humidity	
	Water content of A (%)	Water content of B (%)	Water content of A (%)	Water content of B (%)
0	4.58	4.60	4.58	4.60
12	4.31	4.10	4.65	4.70
24	4.20	3.80	4.67	4.79
36	4.08	3.55	4.69	4.84
48	3.96	3.38	4.72	4.90
60	3.88	3.10	4.77	4.98
72	3.85	2.85	4.79	5.15

From the data in Table 1 it can be seen that the novel azithromycin crystals of this invention of this invention are clearly superior in terms of stability to the azithromycin dihydrate crystals of EPO 298,650.

2. Example of Preparation

2.1 Preparation of azithromycin short columnar crystals of this invention

Hygroscopic azithromycin monohydrate (100 g, water content 2.5%, prepared in accordance with U.S. Patent 4,474,768) was dissolved at 55°C in a mixture of 500 ml of acetone and 500 ml of water, the mixture that was obtained was cooled to room temperature within 1 hour and was allowed to stand for 5 hours, with crystals being precipitated. The crystals were filtered and collected, after which they were washed with acetone/water (1/2) 3 × 100 ml) and then vacuum dried at 20°C to a water content of 4.6 ± 0.2%, with 90.2 g of short, columnar target crystals being obtained.

IR (KBr) (cm^{-1}): 3950, 3480, 2960, 1725, 1664, 1420, 1380, 1250, 1107, 1050, 803, 671.

$[\alpha]^{20}_{D}$ = 45.0°C (C=2, anhydrous ethanol)

Elemental analysis:

Theoretical values (%): C 58.14, H 9.77, N 3.57

Determined values (%): C 58.28, H 9.80, N 3.56

2.2 Preparation of azithromycin short columnar crystals of this invention

Hygroscopic azithromycin monohydrate (100 g, water content 2.5%, prepared in accordance with U.S. Patent 4,474,768) was dissolved at 20°C in 500 ml of acetone, and 100 ml of water was added dropwise into the solution as it was being stirred within 1 hour. Following that, the solution was then stirred slowly for 5 hours, with crystals being precipitated. The crystals were filtered and collected, after which they were washed with acetone/water (1/3) 3 × 100 ml) and then vacuum dried at 25°C to a water content of (4.6 ± 0.3%), with 97.2 g of short, columnar target crystals being obtained. The infrared and elemental analysis data on said crystals were the same as in 2.1.

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[54]发明名称 一种新的阿齐红霉素结晶及其制备方法

[57]摘要

本发明涉及一种新的阿齐红霉素结晶及其制备方法。

权 利 要 求 书

1. 一种阿齐红霉素结晶，其特征在于，该结晶为短柱状。

2. 制备权利要求 1 要求的阿齐红霉素结晶的方法，该方法包括：将阿齐红霉素一水合物于水溶性有机溶剂和水中结晶。

3. 权利要求 2 的方法，其中权利要求 1 的阿齐红素结晶是从阿齐红霉素一水合物在水溶性有机溶剂和水的混合物中结晶得到的。

4. 权利要求 2 的方法，其中权利要求 1 的阿齐红素结晶是将阿齐红霉素一水合物先溶于水溶性有机溶剂，然后再于水中结晶得到的。

5. 权利要求 3 或 4 的方法，其中阿齐红霉素一水合物：水溶性有机性溶剂：水的摩尔比为 1：10—15：30—1500。

6. 权利要求 2 的方法，其中水溶性有机溶剂选自：甲醇、丙酮、*N*，*N*—二甲基甲酰胺，*N*，*N*—二甲基甲酰胺、二甲基亚砜、环丁砜、六甲基磷酰胺、乙腈。二氧六环、乙二醇、二甲醚、哌啶或它们的混合物。

7. 权利要求 6 的方法，其中水溶性有机溶剂选自：丙酮。

8. 权利要求 1 的阿齐红霉素结晶用于制备药物制剂的方法，其包括将权利 要求 1 的阿齐红霉素结晶直接与药用载体或贮形

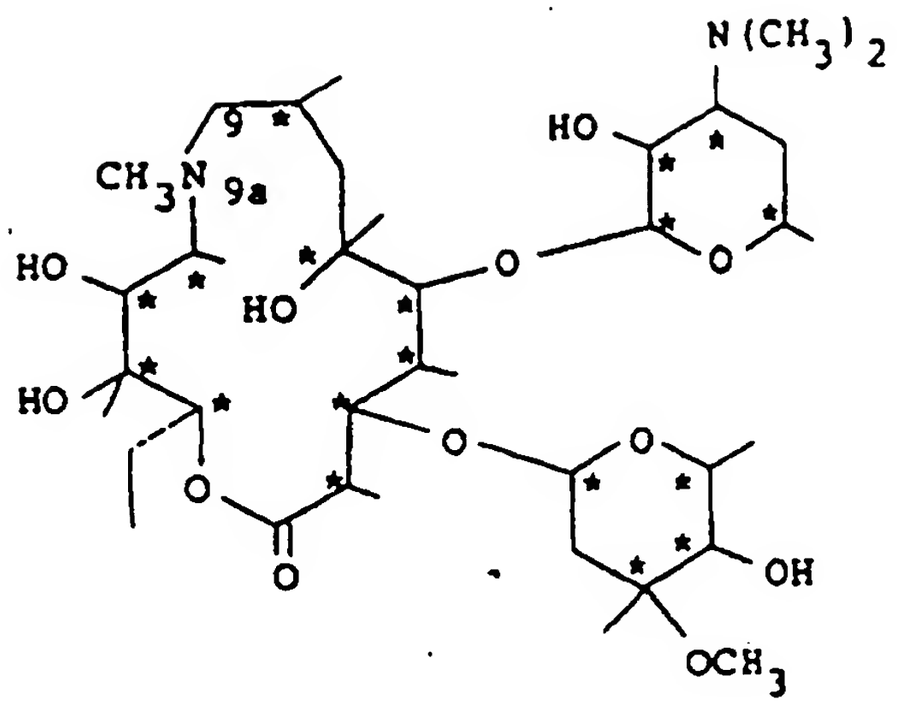
剂混合制成常规药物制剂。

说　　明　　书

一种新的阿齐红霉素结晶及其制备方法

本发明涉及一种新的阿齐红霉素结晶、其制备方法及其用于制备药物制剂的用途。更具体讲，本发明涉及的是一种具有优良流动性和稳定性的阿齐红霉素短柱状结晶，该结晶的制备方法及其用于制备药物制剂的用途。

阿齐红霉素（化学名称为：9—脱氧—9α—氧杂—9α—甲基—9α—高红霉素 A）衍生于红霉素 A，其是一种广谱抗生素。阿齐红霉素与红霉素相比，其具有抗菌谱广，耐酸，利于口服，药物动力学特性理想等优点。阿齐红霉素结构如下面式 I 所示：



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式 I 的阿齐红霉素是一已知化合物。美国专利 US. 4,474,768 和 US 专利 4，517,359 披露了一种制备阿齐红霉素一水合物的方法，但由于阿齐红霉素一水合物的吸湿性，使其在制剂中很不稳定，因而在临床应用中受到很大限制；欧洲专利 EPO,298,650 披露了一种较阿齐红霉一水合物更稳定的阿齐红霉素二水合物及其制备方法。由该方法制备出的阿齐红霉素二水合物为粉状，不能直接用于制剂；另外，该方法所使用的四氢呋喃及 C_6—C_7 脂肪烃试剂较贵，四氢呋喃及 C_6—C_7 脂肪烃之间的沸点相差较小，溶剂回收困难，产品中的含水量不易控制。

本发明的目的是寻找一种具有更好流动性和稳定性的新的阿齐

红霉素结晶及其更简单、经济的制备方法。

本发明者经广泛深入地研究，出人意料地发现：将阿齐红霉素一水合物在水溶性有机溶剂和水的混合物中结晶，可得一种新的短柱状阿齐红霉素结晶，该结晶具有优良的流动性和稳定性，可直接用于药物的制剂中。本发明基于上述发现得以完成。

本发明的第一个目的是涉及一种新的阿齐红霉素结晶，结晶为短柱状结晶，其具有优良的流动性和稳定性，并可直接用于药物制剂的制备中。

更具体讲，本发明新的阿齐红霉素结晶含有 4—6%的水，其具有如下 X—射线衍射特征：

2—THETA	*INT*	*d*	*I/IO*
6.180	111.0	14.290	4
7.820	3292	11.296	11
9.800	29070	9.018	100
11.180	5050	7.908	17
12.420	3638	7.121	13
14.580	1936	6.071	7
15.300	3922	5.786	13
15.660	2262	5.654	8
17.060	2197	5.193	8

18.780	1909	4.721	7
19.000	2783	4.667	8
19.540	1909	4.539	7
19.820	2569	4.476	9
20.400	3600	4.350	12

其红外光谱特征如下：

$IR(cm^{-1})$：3429（OH），2969（$-CH_3$，$-CH_2$，$-CH-$），1728（$C=O$），1459（$-CH_3$，$-CH_2$，$-CH-$），1183（$C-O-C$），1050（$C-OH$，$-C-O-D$）。

本发明新的阿齐红霉素结晶的稳定性实验将在后面的实施例中予以描述。

本发明第二个目的涉及的是制备本发明新的阿齐红霉素结晶的方法，其包括：将阿齐红霉素一水合剂于水溶性有机溶剂和水的混合物中结晶。

更具体讲，本发明的方法是将阿齐红霉素一水合物溶于热有机溶剂和水的混合物中，然后缓慢冷却直到析出结晶，或将阿齐红霉素一水合物溶于有机溶剂，然后缓慢加水直至析出结晶。阿齐红霉素一水合物的溶 解温度和本发明新的阿齐红霉素结晶的结晶温度并不关键，一般自室温至溶剂沸点，优选室温，有机溶剂用量以能使阿齐红霉素一水合物全部溶解为准，所用水的量以能使大部分结

(78%以上)析出为准，一般阿齐红霉素一水合物：有机溶剂：水(摩尔比)＝1：10—15：30—1500。最后过滤结晶，并在室 温真空干燥至水含量 4—6%。

在本发明方法中使用的水溶性有机溶剂选 自甲醇、丙醇、N，N—二甲基甲酰胺，N，N—二甲基乙酰胺，二甲基亚砜、环丁砜、六甲基磷酰胺，乙腈，二氧六环，乙二醇二甲醚，吡啶 以及它们的混合物，其中优选丙酮。

本发明第三个目的涉及的是本发明新的阿齐红霉素结晶在制备药剂中的应用，其包括将本发明新的阿齐红霉素结晶直接用于制备抗生素制剂。

下面的实施例用于进一步描述本发明，但并不意味着本发明仅限于此。

一. 稳定性实验：

将本发明新的阿齐红霉素结晶(后面用 *A* 表示)于相对湿度 20%和相对湿度 90%下室温放置，分别在 0，12，24，36，48，60 和 72 小时检测结晶中水份的变化。于相同条件下，用 *EPO* 298，650 中的阿齐红霉素二水合物结晶(后面用 *B* 表示)做同样实验，结果见表 1：

表 1

本发明阿齐红霉素结晶(*A*)与 *EPO* 298，650 的阿齐红霉素二水合物结晶(*B*)的稳定性对比

表　1

本发明阿齐红霉素结晶(A)与ＥＰＯ　298，650的阿齐红霉素二水化合物结晶(B)的稳定性对比

时　间（小时）	相对湿度２０%		相对湿度９０%	
	A的水份（%）	B的水份（%）	A的水份（%）	B的水份（%）
0	4·58	4·60	4·58	4·60
12	4·31	4·10	4·65	4·70
24	4·20	3·80	4·67	4·79
36	4·08	3·55	4·69	4·84
48	3·96	3·38	4·72	4·90
60	3·88	3·10	4·77	4·98
72	3·85	2·85	4·79	5·15

由上面表 1 中数据可明显看到：本发明的新的阿齐红霉素结晶在稳定性上明显优于 *EPO* 298,650 中的阿齐红霉素二水合物结晶。

二. 制备实施例

2.1. 本发明阿齐红霉素短柱状结晶的制备

将吸湿的阿齐红霉素一水合物（100g，水含量 2.5%，按美国专利 *US.* 4,474,768 制备）在 55℃下溶于 500*ml* 丙酮和 500*ml* 水的混合液中，1 小时内将所得混合物冷却至室温，于室温放置 5 小时析出结晶，滤集结晶，然后用丙酮/水(1/2)3×100*ml* 洗涤，20℃真空干燥至水份 4.6±0.2%，得呈短柱状的标题结晶 90.2g。

IR（*KBr*）（cm^{-1}）：3950,3480,2960,1725,1664,1420,1380,1250,1107,1050,803,671。

$[\alpha]_D^{20}$ = −45.0℃（*C*=2，无水乙醇）

元素分析：

理论值(%)：*C*58.14，*H*9.77，*N*3.57；

实测值(%)：*C*58.28，*H*9.80，*N*3.56。

2.2. 本发明阿齐红霉素短柱状结晶的制备

将吸湿的阿齐红霉素一水合物（100g，水含量 2.5%，按美国专利 *US.* 4，474,768 制备）在 20℃溶于 500*ml* 丙酮，在 1 小时内随搅拌往其中滴加 100*ml* 水。然后再缓慢搅拌 5 小时，析出结晶，滤集结

晶，用丙酮/水(1/3) 3×100ml 洗涤，25℃真空干燥至水份(4.6±0.3%)，得呈短柱状的标题结晶 97.2g。该结晶的红外和元素分析数据同 2.1 中的。